0.06 log eu/mL, p=0.04). LPS concentration was associated with body fat (r=0.62, p=0.003), Lactobacillus spp. 16s rRNA gene copy number (r=-0.60, p=0.009), and six serum inflammatory markers: GCSF (r=-0.49, p=0.03), serum IL-1α (r= -0.48, p=0.048), IL-4 (r=-0.52, p=0.02), IL-6 (r=-0.49, p=0.03), IL-13 (r=-0.59, p=0.007), IFNγ (r=-0.49, p=0.03). Together, Methanobrevibacter spp. and Lactobacillus spp. levels had a strong relationship predictive with Modified Mankin Scores when evaluated using linear regression modelling (r2=0.50, p<0.001).
Conclusions: We found that body fat, not body mass, was associated with OA damage, and that a distinct inflammatory signature in serum and synovial fluid differentiates obese from lean animals. The source of this inflammation remains to be determined. However, several significant relationships between the gut microbiota and local and systemic inflammatory markers were identified. Therefore, we propose that the link between joint damage and microbiota may be associated with LPS, which also could explain, in part, the inflammatory signatures evaluated here. Further work is warranted.

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A ROLE FOR CC-CHEMOKINE RECEPTOR 7 (CCR7) IN A MURINE MODEL OF OSTEOARTHRITIS: IMPACT ON JOINT STRUCTURE AND FUNCTION

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Purpose: Synovial inflammation is a common but variable feature of knee osteoarthritis (OA) associated with more severe joint symptoms and progression of cartilage erosion. However, it is unclear whether prevention or treatment of synovial inflammation will diminish development of OA. In order to identify potential targets for modification of synovial inflammation, we previously analyzed synovial gene expression patterns in patients with meniscal tears. We identified a set of chemokine transcripts associated with inflammation, which included the chemokine receptor CCR7 and its two ligands CCL19 and CCL21. CCR7 plays a central role in development of chronic inflammation. The current study was undertaken to determine if CCR7 plays a mechanistic role in development of OA-related structural and functional manifestations using a murine model of knee OA induced by meniscal destabilization.
Methods: To confirm expression of CCR7 in human disease, knee synovial tissues from 15 patients with meniscal tears, 13 patients with advanced knee OA, and 9 organ donors without a history of chronic knee symptoms (asymptomatic donors) were collected through IRB-approved biorepositories. CCR7 expression was examined by immunoperoxidase staining and automated image analysis. To investigate effects of CCR7 loss in vivo, genetically modified mice lacking expression of CCR7 (CCR7-/-), backcrossed onto the C57BL/6 background, were obtained from Jackson Laboratory. CCR7-/- and C57BL/6 controls were subjected to DMM surgery (destabilization of the medical meniscus) at 10-12 weeks of age. Six weeks after surgery, groups of 5 mice were sacrificed and knee joints evaluated histopathologically for cartilage degeneration and osteophyte formation using standard methods. Changes in spontaneous locomotion and behavior were investigated longitudinally (up to 16 weeks) after DMM surgery, using the LABORAS® laboratory animal behavior analysis system (Metris B.V., Hoofdorp, The Netherlands).
Results: CCR7 staining in synovial tissues was significantly higher in patients with meniscal tears (Mean % area +/- SEM = 12.26 +/- 2.4) compared to asymptomatic donors (3.55 +/- 2.7, p=0.01). Six-weeks after DMM surgery, CCR7-/- mice exhibited reduced cartilage degeneration (Mean +/- SEM = 1.60+/-0.81) and osteophytes (0.80+/-0.20) compared to C57BL/6 controls (cartilage = 5.20+/-1.06, osteophyte = 1.40+/-0.24, p<0.0001). Decreases in climbing activity post-operatively were observed in WT mice by 4 weeks post-DMM,and sustained up to 8 weeks. In contrast, CCR7-/- mice maintained pre-operative levels of climbing activity post-DMM.
Conclusions: In the DMM model of OA, mice deficient in CCR7 showed reduced structural and functional manifestations of joint degeneration. Whether these effects are mediated by reductions in synovial inflammation will be investigated in future studies. Targeted anti-inflammatory treatments aimed at blockade of CCR7 or its ligands should be tested for both structure- and symptom- modifying effects in future studies.

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MIA-INDUCED INFLAMMATION AND JOINT PAIN ARE REDUCED IN TRPA1 DEFICIENT MICE – POTENTIAL ROLE FOR TRPA1 IN OSTEOARTHRITIS

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Purpose: Injection of monosodium iodoacetate (MIA) into a murine joint is a widely used experimental model of osteoarthritis (OA). MIA induces an acute inflammation which leads to destruction of articular cartilage, to hyperalgesia and to decreased weight bearing on the affected limb indicative for pain. Like in the OA, the detailed mechanisms related to the onset and progression of MIA-induced experimental OA are not understood thoroughly. However, on cellular level MIA has been recognized to inhibit glyceraldehyde-3-phosphate leading to production of reactive oxygen species (ROS) and to activation of caspases and inflammatory gene expression.
Transient Receptor Potential Ankyrin 1 (TRPA1) is an ion channel known to mediate nociceptive signals and neurogenic inflammation. It is activated by various environmental pungent compounds but also by molecules produced in inflammation such as ROS. In the present study we tested the hypothesis that TRPA1 is involved in MIA-induced acute inflammation and joint pain.
Methods: The effects of pharmacological inhibition (by TCS 5861528) and genetic depletion of TRPA1 were studied in MIA-induced inflammation and joint pain (weight-bearing test) in mouse models. In addition, the effect of MIA was studied in human primary OA chondrocytes and in mouse cartilage.
Results: Intra-articularly injected MIA provoked spontaneous weight shift away from the affected limb in wild type but not in TRPA1 knockout mice referring alleviated joint pain in TRPA1 deficient animals. Interestingly, mice treated with the selective TRPA1 antagonist TCS 5861528 as well as TRPA1 deficient mice developed tempered inflammatory response when MIA was injected into the paw indicating that TRPA1 is involved in the mechanisms of MIA-induced acute inflammation. Also, the levels of substance P were diminished in TRPA1 KO mice and in mice treated with the TRPA1 antagonist, and the MIA-induced acute response was attenuated by pre-treatment with the neurokinin 1 receptor antagonist L703,606. Further, cultured human primary OA chondrocytes expressed TRPA1. Co-stimulation with MIA and IL-1β increased COX-2 expression which was inhibited by a selective TRPA1 antagonist, and COX-2 expression was also lower in the cartilage from TRPA1 knock-out than wild type mice.
Conclusions: TRPA1 mediates MIA-induced inflammation and pain in experimental models supporting the role of TRPA1 as a potential mediator and drug target in OA.

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BONE MARROW LESIONS ARE ASSOCIATED WITH LOCAL HISTOLOGICAL SYNOVITIS AND SYMPTOMS IN PATIENTS WITH END-STAGE KNEE OSTEOARTHRITIS: A CROSS-SECTIONAL STUDY

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Purpose: Osteoarthritis (OA) of the knee is a slowly progressive age-related joint disease, which is initially characterized by articular cartilage degradation. Although OA was considered to be a non-inflammatory condition, the role of synovitis in OA has attracted particular attention. Recently it is considered that synovial inflammation could play an important role in the pathophysiology of OA. We previously reported that the cytokine profiles expressed in synovium in end-stage knee OA were different from those expressed in synovium in early-stage knee OA. We also previously revealed the symptoms of patients with end-stage of knee OA who required total knee arthroplasty (TKA) showed a significant correlation with the severity of synovitis in affected knee joint. On the other hand, no joint structural changes evaluated by classic radiography were indeed associated with the pain and symptoms of the patients in our previous study. In addition, it's still